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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS

In re application of

Kobrehel, et al. Art Unit: 122

Serial No.: 304,481 Examiner: Chen

Filed: September 22, 1981

For: NEW ERYTHROMYCIN A COMPOUNDS, A PROCESS FOR THE MANUFACTURE THEREOF AND THE USE OF THE NEW COMPOUNDS IN THE CONTROL OF BACTERIA

606-82

APPEAL BRIEF

Honorable Commissioner of Patents and Trademarks
Washington, D.C.

Sir:

This is an appeal from the final rejection of claims 3-11. The appeal from the final rejection of claim 23 is hereby withdrawn. Claim 2, the remaining claim in the application, has been allowed.

CLAIMS ON APPEAL

3. 2'-acetyl-N-methyl- 11-aza-10-deoxo-10-dihydro erythromycin A.

4. 2',4"-diacetyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A.

5. 2'-propionyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A.

6. 2',4"-dipropionyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A.

7. N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate.

8. 2'-acetyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate.

9. 2',4"-diacetyl-N-methyl-11-aza-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate.

10. 2'-propionyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate.

11. 2',4"-dipropionyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate.

DESCRIPTION OF INVENTION

The present invention is concerned with new erythromycin A compounds. The compounds exhibit antibacterial activity. The compounds of the present invention are N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A and certain derivatives thereof. The N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A is the subject of allowed claim 2. The presence of the N-methyl group provides compounds which have improved activity and/or reduced toxicity and/or increased stability when compared to compounds without the N-methyl group.

REFERENCE RELIED UPON BY EXAMINER

U.S. Patent 4,328,334 of May 4, 1982 to Kobrehel, et al., filed March 28, 1980.

REJECTION OF CLAIMS

Claims 3-11 are rejected under 35 U.S.C. 103 as being unpatentable over U.S. Patent 4,328,334 to Kobrehel, et al.

APPLICANTS' RESPONSES

TO REJECTION OF CLAIMS

Claims 3-11 are rejected under 35 U.S.C. 103 as being unpatentable over U.S. Patent 4,328,334 to Kobrehel, et al. Kobrehel, et al. fail to suggest or render obvious the present invention since the R_1 group suggested by Kobrehel, et al. does not encompass the methyl group, as required by the present invention. Instead, R_1, according to Kobrehel, et al., can be hydrogen, an alkanoyl, or a 4-R-Ph-SO_2 group. However, it has been found, according to the present invention, that the presence of the N-methyl group provides compounds which have improved activity, and/or toxicity, and/or stability as compared to the compounds disclosed by Kobrehel, et al.

Along these lines, Tables 3-7, Figure 1, and accompanying Declaration were filed along with a Response After Final. In view of these materials, claim 2, which is concerned with N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A, was allowed. The N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A and N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate are the closest of the compounds of the present invention to the specific examples in U.S. Patent 4,328,334.

Concerning the N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate, which is the subject of claim 7, the Board's attention is kindly directed to the Table 4 (copy attached) presented along with the response filed after final rejection.

With respect to Table 4, the in vitro potentcies of N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A and its 13,14-cyclic carbonate derivative of claim 7 (i.e., N-methyl-11-aza-10-deoxo-10-dihydro-erythromycin A 13,14-cyclic carbonate) were tested in comparison with

erythromycin A and its 11-aza derivative against 179 gram-negative organisms. Out of 179 gram-negative organisms, 64 (35.8%) were resistant to erythromycin A, 22 (12.3%) were resistant to 11-aza-10-deoxo-10-dihydro erythromycin A and only 14 (7.8%) were resistant to the N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate of the present invention.

Also, as evidenced by said Table 4, N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate, similarly to the allowed N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A, in therapeutic concentrations of 0.5-4.0 mcg/ml inhibited about 30% more strains than the starting 11-aza-10-deoxo-10-dihydro erythromycin A.

Also, in view of the somewhat superiority in the antibacterial activity of 11-aza-10-deoxo-10-dihydro erythromycin A, as compared to 11-aza-10-deoxo-dihydro erythromycin A 13,14-cyclic carbonate shown in Table 1 in U.S. Patent 4,328,334 (compare Examples I and VI) it is reasonable and logical to attribute the improved results of the compound of the claims to the presence of the N-methyl substituent.

Additional indicia of the nonobviousness of the present invention are the antibacterial results reported in Tables 1 and 2 on pages 5 and 6, respectively, of the specification (copy attached) which not only show the results achieved by the compound of allowed claim 2 and that of its 13,14-cyclic carbonate (claim 7), but also favorable results from the following compounds:

2'-acetyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A (claim 3)

2'4"-diacetyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A (claim 4)

2'-propionyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A (claim 5)

2',4"dipropionyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A (claim 6)

2'-acetyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate (claim 8)

2',4"-diacetyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate (claim 9)

2'-propionyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate (claim 10)

2',4"-dipropionyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate (claim 11)

Accordingly, in view of the above comparative tests which compare what is believed to be the closest compounds of the present invention to what is deemed to be the closest prior art compound specifically employed in an example in U.S. Patent 4,328,334 and in view of the other evidence in the application, as filed, the nonobviousness of the claimed compounds has been established. To require additional testing between those compounds of the present invention which are more remote from the specific examples in U.S. Patent 4,328,334 is not warranted.

The evidence already presented clearly demonstrates that the improved results are attributable to the presence of the N-methyl substituent as required by each and every claim. Along these lines the Board's attention is kindly directed to In re Cescon, 474 F.2d 1331 (CCPA 1973) and In re Papesch, 315 F.2d 381 (CCPA 1963). For instance, in the case of In re Papesch, the affidavit relied upon compared the prior art trimethyl compound and the trimethyl compound within the scope of the invention. However, the claims in said case included trialkyl compounds other than trimethyl and yet, the affidavit was deemed adequate to establish nonobviousness. Accordingly, it seems clear that the evidence already presented herein is sufficient to establish the patentability of claims 3-11.

CONCLUSION

In view of the above, it is submitted that the Examiner erred in the final rejection of claims 3-11 and accordingly, it is requested that the Board of Appeals reverse the Examiner.

Attached hereto are two copies of an authorization to charge $115.00 to our Deposit Account No. 22-0185 for the Appeal Brief fee.

Respectfully submitted,

Date: 5-9-84

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TABLE 1

Minimum Inhibitory Concentrations (MIC)

Test Strains	Results expressed in mcg/ml Standard	1	2	3	5	6+
Streptococcus faecalis ATCC 8043	0.05	0.01	0.1	0.5	0.05	0.1
Staphylococcus epidermidis ATCC 12228	0.5	0.5	0.5	2.5	0.05	0.1
Staphylococcus aureus ATCC 6538-P	0.5	0.5	0.5	0.5	0.1	0.5
Micrococcus flavus ATCC 10240	0.05	0.01	0.5	0.1	0.05	0.5
Sarcina lutea ATCC 9341	0.05	0.05	0.1	0.1	0.05	0.05
Bacillus cereus var. mycoides ATCC 11778	0.5	0.5	0.5	0.5	0.5	0.5
Bacillus subtilis ATCC 6633	0.5	0.1	0.1	2.5	0.5	0.1

Standard: 11-aza-10-deoxo-10-dihydro erythromycin A

1 = N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A (allowed claim 2)

2 = 2'-acetyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A (claim 3)

3 = 2',4"-diacetyl-N-methyl -11-aza-10-deoxo-10-dihydro erythromycin A (claim 4)

5 = 2'-propionyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A (claim 5)

6 = 2',4"-dipropionyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A (claim 6)

+ = The Arabic figures correspond to the notation of the examples

TABLE 2

Minimum Inhibitory Concentrations (MIC)

Test strains	Results expressed in mcg/ml 7	8	9	10	11 +
Streptococcus faecalis ATCC 8043	0.05	0.05	0.5	0.1	0.1
Staphylococcus epidermidis ATCC 12228	0.5	0.5	2.5	0.5	2.5
Staphylococcus aureus ATCC 6538-P	0.1	0.1	2.5	0.5	2.5
Micrococcus flavus ATCC 10240	0.1	0.1	1.0	0.5	0.5
Sarcina lutea ATCC 9341	0.1	0.05	0.1	0.05	0.05
Bacillus cereus var. mycoides ATCC 11778	0.1	0.1	2.5	0.5	1.0
Bacillus subtilis ATCC 6633	0.1	0.1	2.5	1.0	1.0

7 = N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate (claim 7)

8 = 2'-acetyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate (claim 8)

9 = 2',4"-diacetyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate (claim 9)

10 = 2'-propionyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate (claim 10)

11 = 2',4"-dipropionyl-N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate (claim 11)

+ = The Arabic figures correspond to the notation of the examples.

TABLE 4

Antibacterial *In Vitro* Activity on
Gram-Negative Clinical Isolates

TEST ORGANISM	COMPOUND	MIC (mcg/ml) 0.5	1.0	2.0	4.0	8.0	16.0	32.0	64.0	128.0	R	No.
	E					2	28	40	8		22	100
E. coli	A	1		2	39	50	2	1	2		3	
	1		4	42	45	5	2	1	1		0	
	7		2	37	53	3		1	2		2	
	E						1	2	2		4	9
Klebsiella	A				3	1	3	1			1	
pneumon.	1				4	4	1					
	7					2	4	1	2			
	E						1		2		7	10
Klebsiella	A					3	5				2	
aerogenes	1					9		1				
	7					5	1	3			1	
	E					13					3	16
Proteus	A					2		3	1		10	
mirabilis	1				1	2	1	10			2	
	7				2		1		6		7	
	E								1		9	10
Pseudomonas	A					1		2	3		4	
aerug.	1					1		1	5		3	
	7						1	4	1		4	
	E								1		17	18
Enterobacter	A					1	5	7	4		1	
aerog.	1				3	6	6	2			1	
	7					3	9	1	5			

TEST ORGANISM	COMPOUND	MIC (mcg/ml) 0.5	1.0	2.0	4.0	8.0	16.0	32.0	64.0	128.0	R	No.
	E						1					1
Enterobacter	A					1						
liquef.	1				1							
	7					1						
	E						1				2	3
Mima	A							2	1			
polymorpha	1					1		1	1			
	7					1	1	1				
	E					1	3	1	1			6
Herella	A		1				1	3			1	
	1		1	1			3	1				
	7			1	2	2			1			
	E	1		2	3							6
Haemophylus	A	1	3	2								
influ.	1	3	3									
	7	1	4	1								
	E	1	0	2	3	16	35	45	15		46	179
Number of	A	2	4	4	42	59	16	19	11		22	179
sensitive	1	3	8	43	54	28	13	17	7		6	179
strains	7	1	6	39	57	17	17	11	17		14	179

E = Erythromycin A

A = 11-aza-10-deoxo-10-dihydro erythromycin A

1 = N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A

7 = N-methyl-11-aza-10-deoxo-10-dihydro erythromycin A 13,14-cyclic carbonate

Method: Two-fold serial dilution technique in MH agar.

R = resistant

No. - Number of tested strains.